EEG in connection with coma

BACKGROUND Coma is a dynamic condition that may have various causes. Important changes may take place rapidly, often with implications for treatment. The purpose of this article is to provide a brief overview of EEG patterns for comas with various causes, and indicate how EEG can contribute to an assessment of the prognosis for coma patients.

METHOD The article is based on many years of clinical and research experience with EEG in connection with coma states. A self-built reference database was supplemented with searches in PubMed for relevant articles.

RESULTS EEG reveals immediate changes in coma, and can provide early information on cause and prognosis. It is the only diagnostic tool for detecting non-convulsive epileptic status. Locked-in syndrome may be overlooked without EEG. Repeated EEG recordings increase diagnostic certainty and make it possible to monitor coma developments.

INTERPRETATION EEG reflects brain function continuously and therefore holds a key place in the assessment and treatment of coma.

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MAIN POINTS

EEG holds a central place in the assessment and treatment of coma

Repeated EEG recordings may be useful in connection with coma irrespective of cause

Some causes and complications of coma can only be diagnosed with the aid of EEG

The word «coma» stems from Greek, and means deep sleep. The term is first found in the works of Hippocrates (ca. 460–370 BC) and subsequently of Galen (129–199 AD) (1). The term is used again by Thomas Willis (1621–1675). He localised the state of lethargy (Gr. lethe = forgetfulness) and argos (Gr. = lazy) in the cortex and that of coma beneath the cortex (i.e. subcortically) (1). With von Economo's (1876– 1931) finding of lesions in the hypothalamus of patients who died of encephalitis lethargica (2) and the subsequent finding of the ascending reticular activating system (3), it became clear that coma could be caused by affection of all these structures (see illustration).

Damage to the cortex can affect integration of information, resulting in confusion, hallucinations or memory problems, without the degree of wakefulness necessarily being affected. However, a diffuse cortical affection may cause reduced consciousness, depending on how much of the cortex is affected. An injury that affects the activating systems in the brain stem, midbrain or thalamus may be small, but may cause a deep coma.

Today the word coma means a pathological state of suspended consciousness and unresponsiveness to external or internal stimuli (4). The state can last for anything from hours to weeks and change to the regaining of consciousness with or without sequelae, to death or to a permanent state where the patient may be «awake», but without (or with a minimal amount of) awareness, known as a chronic vegetative state (4).

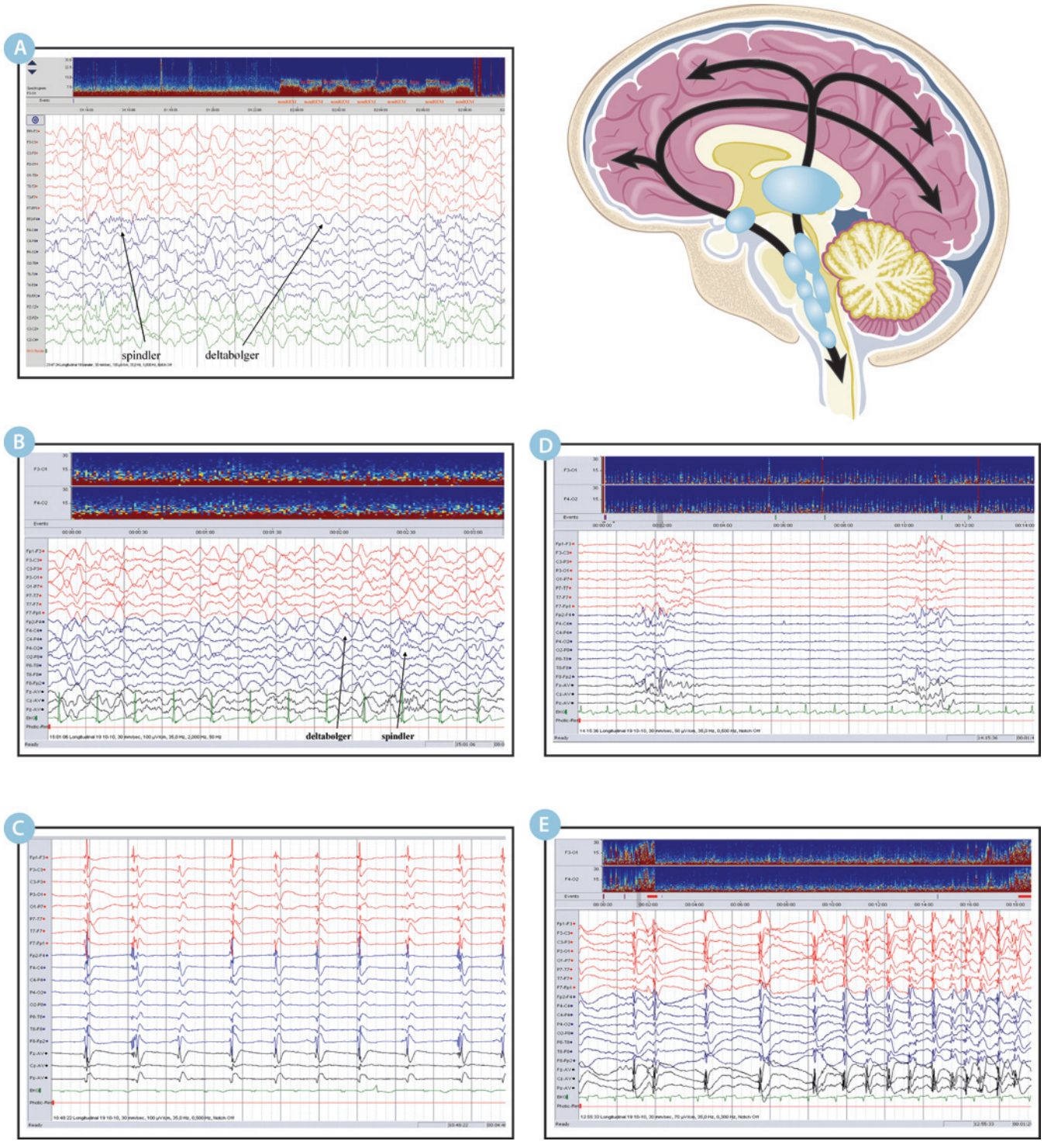
An overview of clinical diagnosis, gradation and causes of coma is beyond the scope of this review. For this we recommend a very good review by Young (5). In the present article we seek to provide a principle understanding of electroencephalography (EEG), with an outline of the basic physiology and some simple pathophysiological observations. We will also present an overview of EEG findings with known prognostic value for coma states and an overview of findings that have implications for treatment.

Method

The overview is based on the authors' extensive clinical and research-related experience of EEG in comatose patients and a discretionary selection of relevant articles on EEG in connection with coma. The articles were selected from a self-built literature database and supplemented by searches for relevant articles in PubMed. The search was concluded in October 2011.

What does a scalp EEG measure?

An electrocardiogram that is recorded by means of electrodes attached to the skin of the head is called a scalp EEG. The excitatory pyramidal cells of the cerebral cortex are organised in functional columns at right angles to the surface. The electrical activity in these cells generates field potentials through interaction with inhibitory interneurons. The potentials are an expression of the total synaptic activity (6). Inhibition and excitation in the neurons and the neuronal networks cause the field potentials to synchronise and oscillate at different frequencies and voltages (7). The fewer the neurons oscillating in small networks, the higher the frequency and the lower the voltage. It is this activity which is measured in an EEG. Some of the activity can be registered by means of electrodes attached to the scalp, but intracranial electrodes are required to register the smallest, most rapid oscillations.



The top right shows an anatomical illustration of the ascending reticular activating system, which consists of two parts: the ventral part, which goes through the hypothalamus, and the dorsal, which goes through the thalamus. There are five EEG printouts: A) EEG for normal sleep. The uppermost blue panel shows the frequency spectrogram (predominant frequencies along the Y-axis and time along the X-axis) through the recording, in this case throughout a 24-hour period. The last half shows the sleep period, with seven REM/NREM cycles. The EEG sequence shows 12 seconds of NREM sleep, with spindles and delta waves. Red is from the left and blue from the right side of the head. B) EEG from patient with acute demyelinising encephalomyelitis in the upper brain stem. EEG shows persistent deep sleep with preserved cortico-thalamic interaction (compare with printout A), but without reactivity. No alternation is seen between NREM and REM sleep (see uppermost panel with 3.5-hour spectrogram) because the REM-NREM alternation is regulated by the upper brain stem. C) EEG with status myoclonicus from patient who had been resuscitated after cardiac arrest. D) EEG from another patient who had been resuscitated after cardiac arrest. EEG shows low voltage with burst-suppression. E) EEG from patient who had been resuscitated after cardiac arrest. Periodic activity and nonconvulsive status epilepticus are seen here. The spectrogram shows a period of 18 minutes of periodic activity preceded and followed by two shorter sequences of continuous epileptic activity (marked with red). Illustration © Illumedic

During sleep, the interaction of the cortex, thalamus, hypothalamus and brain stem generates slow oscillations that may involve all the neurons in large networks (8–10). This is of relevance to coma diagnosis.

In a scalp EEG recorded in relaxed, awake condition and with closed eyes, activity with a frequency of 8–13 cycles per second (alpha activity) predominates over the posterior areas of the head. Rapid activity with a frequency of 13–30 cycles per second and low voltage predominates over the anterior areas of the head (beta activity). During light sleep, slower activity of 4–7 cycles per second predominates (theta activity). During deeper sleep (non-rapid eye movement sleep, NREM) spindle-shaped sequences of 10–16 cycles per second predominate (sigma or spindle activity) and slow activity of 1–4 cycles per second (delta activity) with higher voltages. Both are modulated by slow background oscillation of 0.2–1 cycle per second. NREM sleep alternates with REM sleep in periods of about 70–80 minutes (illustration, EEG printout A).

Cortical dysfunction

Diffuse cortical dysfunction can reduce synaptic activity, damage networks and disturb the balance between excitation and inhibition. This usually causes the proportion of slow waves in the EEG to be larger than normal. When excitatory mechanisms predominate, however, aberrant rhythms may arise, such as periodic or persistent triphasic waves or clear epileptic activity. Pronounced cortical hyperexcitability or disinhibition may be expressed in EEGs as generalised epileptic activity, and in some cases may be an independent cause of reduced consciousness. EEG changes of this kind are seen largely when coma has hypoxic, metabolic or toxic causes. They can also be seen with various progressive encephalopathies that end in coma, such as Creutzfeldt-Jakob disease (11, 12).

Subcortical white matter

Damage to the subcortical white matter results in functional disturbances in the cortex due to deafferentation of the cortical areas concerned. These will then show a tendency towards pathological hypersynchronisation (9). In EEGs this is seen as intermittent slow waves of relatively high amplitude, at frequencies of 3–7 per second. Broadly speaking, the deeper the lesion, the slower and more high voltage the waves and the larger the area where they occur. If the damage also affects the cortex, the rhythms may become epileptiform. EEG changes of this kind may be seen after contusions, intracerebral haemorrhages, infarctions, tumours and encephalitis. The degree of alteration of consciousness depends on how much and which region of the cortex is deafferentated (13). Expanding intracranial processes, such as tumours, haemorrhages or abscesses, may also reduce consciousness by affecting the activating systems in the upper brain stem and midbrain (14). Repeated EEG recordings may reveal such a development.

Thalamus, hypothalamus, mesencephalon and brain stem

The corticothalamic system is involved in a continuous interaction, which varies over a 24-hour period, with the mesencephalic and hypothalamic sleep regulation systems, with the frontobasal activating system and with the reticular activating system (15). The cortical activity is in constant interaction with the thalamus (16). This is visible in the EEG as characteristic patterns during sleep. The patterns can provide an indication of which systems are affected.

Extensive damage to the upper brain stem may appear in the EEG almost like deep physiological sleep. However, with damage of this nature the whole corticothalamic system and the frontobasal activating system in the hypothalamus will be deafferentated. The sleep-physiological corticothalamic interaction may nonetheless be preserved. The EEG of such a coma does not differ from physiological sleep, but the patient cannot be woken (illustration, EEG printout B).

Sometimes the dorsal and ventral activating systems may be affected to different degrees. This is manifested in the EEG as different reactivity to sensory stimuli. This may result in either a general activation with faster waves or a «paradoxical» activation with intervals of slow waves. Such activity is often rhythmic, high voltage and paroxysmal. A complete absence of activating effect implies more extensive affection. This is normally a bad sign.

Alpha coma

Damage to the pons often affects consciousness. If the pontine tegmentum is also affected, the EEG may show persistent bilateral rhythmic activity. The patient is then in a so-called alpha coma, theta coma or alpha-theta coma, depending on the dominant rhythm frequency. This type of activity predominates over the posterior areas of the head. This type of «rhythmic coma» can also be seen after hypoxic damage. Alpha and theta rhythms then predominate over the anterior areas and are not reactive to sensory stimuli (17, 18).

Locked-in syndrome

If the damage is limited to the ventral pons and does not involve the pontine tegmentum, the patient may be fully conscious, but deafferentated. The patient is then mute and almost completely paralysed. However, vertical eye movements and blinking are preserved and become the only means of communication (19, 20). This is a very frightening condition for the patient. In such cases the EEG shows normal reactive alpha activity when the patient is awake. Sleep physiology is also preserved on the EEG. Extensive polyradiculitis (Guillain-Barré syndrome) and critical illness myopathy/neuropathy may also cause a similar condition (21).

It is very important clinically that locked-in syndrome is not mistaken for alpha coma. EEG is thus essential for distinguishing between these two states.

Ischaemic coma

With ischaemic coma, a wide range of changes can be seen in EEGs (22, 23). The brain's cortical pyramid cell system is most vulnerable to ischaemia, but there may be large individual variations. Hypoxia may have developed rapidly, as with cardiac arrest, or more slowly, as with respiratory arrest, with initially preserved cerebral perfusion. Different medicines may also affect the brain's susceptability to ischaemia. Body temperature may be an important factor, as with drowning accidents or other forms of hypothermia. Some areas of the brain may also be more susceptible due to arteriosclerosis with reduced perfusion.

In an EEG this may result in different degrees of diffuse cortical functional impairment without excitatory elements. Hyperexcitability, or disinhibition, is also common, however. This may cause epileptiform changes, varying in type and extent, such as spiked triphasic waves or periodic or persistent epileptic activity (24). Generalised epileptic activity may take the form of a so-called status myoclonicus pattern on the EEG (the term «generalised periodic epileptiform discharge – GPED» is often used now) (illustration, EEG printout C). Such a condition results in persistent myoclonia which do not respond to anti-epileptic drugs. The condition can only be brought to an end by such deep sedation that the EEG becomes «flat», but this does not improve the prognosis. It should be noted that EEGs may also show changes of this nature when the patient does not have myoclonia. Conversely, a patient may have myoclonia without such changes appearing on the EEG. These variations are assumed to express the fact that cortical layers are affected in different ways (25).

Burst-suppression

In cases of very extensive anoxic damage there will be signs of combined metabolic failure and cortical disinhibition (26). This is called «burst-suppression» pattern. When this is due to anoxic damage, it is normally a terminal EEG phenomenon (illustration, EEG printout D). The termination of cortical synaptic activity results in «flat» EEGs. However, it should be noted that deep sedation and deep hypothermia – particularly in combination – may also cause both «burst suppression» and «flat» EEGs.

Repeated EEG is useful

When coma lasts for hours or days, metabolic changes take place with corresponding changes in the EEG picture. Repeated EEG

examinations may be useful, partly for evaluating a prognosis, partly because epileptic activity that requires treatment may occur along the way.

Nonconvulsive status epilepticus

Nonconvulsive status epilepticus exists when the EEG shows persistent epileptic activity without the comatose patient presenting motoric symptoms. The diagnosis is used when the phenomenon is seen in a patient with epilepsy who has entered a protracted state of reduced consciousness or confusion. In rare cases, the patient may be in a coma exclusively as a result of this. The state can only be diagnosed by means of EEG.

The diagnosis can also be used for patients who are in a coma for some reason other than known epilepsy. It is important to distinguish this from nonconvulsive status epilepticus in patients with epilepsy (27–30).

Nonconvulsive status epilepticus may occur in comatose patients during the course of the illness and may exacerbate the prognosis. Such a state should induce attempts at treatment with a non-sedatory antiepileptic drug. At best, the patient may awaken, concurrently with improvement in the EEG. Unfortunately, the EEG finding is often a subsidiary phenomenon to the cause of the coma, and is frequently a sign of serious damage with a very poor prognosis.

Nonconvulsive status epilepticus may yield different EEG patterns, depending on the underlying cause. A hypoxic injury will as a rule result in generalised EEG changes. Encephalitis, cerebral contusion or cerebral infarction will result in focal or lateralised epileptic EEG changes. Periodic spiking is perceived by some as interictal epileptic activity, since it sometimes shows a transition to nonconvulsive status epilepticus (illustration, EEG printout E), whereas others regard it as an ictal phenomenon (31, 32) which may improve the prognosis if it is treated (33). When considering such periodic activity, one should nevertheless be on the watch for the development of nonconvulsive status epilepticus. Sometimes the condition has to be treated with deep sedation with EEG monitoring until the burst-suppression pattern appears (33).

The risk of developing nonconvulsive status epilepticus is relatively high in coma irrespective of cause (34). This stresses the importance of EEG for comatose patients.

Brain death and chronic vegetative state

In Norway, EEG is not used to diagnose brain death in order to terminate treatment or prepare for organ donation. An EEG is nevertheless often taken in such a connection, and is therefore mentioned briefly here. Total cortical destruction is manifested by the absence of activity in a scalp EEG.

When an EEG is taken, hypothermia below 32 °C, circulatory shock and sedation must be excluded. The cause must be known, and clinical signs of brain death must have existed for 12 hours, but this can be reduced to six hours if it has been established that the cause is irreversible (35, 36).

Patients in a chronic vegetative state, i.e. without awareness, but with preserved brain stem structures that maintain autonomic functions, may sometimes lack visible cortical activity in a scalp EEG. However, the majority show EEG activity that is very low voltage, slow, irregular and nonreactive to sensory stimuli. There is no variation in the EEG over a 24-hour period even if the patient clinically exhibits daily cycles of sleeping and wakefulness.

Psychogenic or simulated coma

In rare cases one is faced with an apparently unconscious patient with otherwise normal clinical neurological status. Should there be any doubt as to whether the patient is in a coma, an EEG can reveal normal wakefulness. Thus other, resource-intensive diagnostics can be avoided.

Prognostic assessments

When faced with a comatose patient, it is important to be able to decide whether maximum and resource-intensive treatment should be started or continued (37). EEG has a place in these assessments, not least because it requires limited resources, can be repeated without restrictions and reflects functional changes in the brain.

If the prognosis is to be assessed, the cause of the coma must have been established and the coma must have lasted for at least 24 hours. The patient must not be sedated, hypothermic below 32 °C or in circulatory shock. Only EEGs taken in cases of coma following cardiac arrest have virtually unambiguous prognostic value (38, 39). In cases with other causes, particularly traumatic injury, caution should be observed with respect to making a prognosis on the basis of EEG alone. But with this reservation, the following prognostic factors may nevertheless be postulated (38, 39):

- «Burst-suppression» and status myoclonicus imply a very poor prognosis for survival, but cases have been seen of relatively good restitution after status myoclonicus.
- With non-reactive rhythmic coma (alpha or theta) restitution to a state of self-sufficiency is extremely rare, and as a rule the end is death or a chronic vegetative state.
- Persistent generalised low-voltage, slow activity that is nonreactive to sensory stimuli implies a high mortality rate or survival with very poor neurological restitution.
- Periodic activity in the form of persistent periods of single waves or short, often spiked complexes laterally or bilaterally, at 1–2 second intervals are signs of serious damage. Any survival is then usually with poor neurological restitution.

BOX 1

Synek's gradation of EEG changes associated with coma (41)

Grade 1	Predominantly post-central alpha activity, some theta activity
Grade 2	Predominantly reactive theta activity
Grade 3	Predominantly extensive delta activity or low-amplitude, irregular and non-reactive delta activity
Grade 4	Burst-suppression, generalised epileptic activity (including status myoclonicus), non-reactive low-amplitude activity, alpha coma and theta coma
Grade 5	No visible EEG activity with high sensitivity recording

The general rule for all coma-related EEG pathology is that lack of reactivity to sensory stimuli is a bad sign, unless the coma is due to deep sedation/anaesthesia (40). Several gradation systems have been developed for EEG findings to assist in making prognoses. The most widely used is Syneks gradation, which is simple and has proved highly accurate (41) (Box 1).

Conclusion

EEG can provide early information about the cause of and prognosis in coma states. Repeated EEG recordings increase the diagnostic reliability and make it possible to follow developments in the coma, partly in order to assess a prognosis, partly because epileptic activity requiring treatment may occur along the way. The risk of developing nonconvulsive status epilepticus is relatively high in comas irrespective of cause (34). This stresses the importance of EEG for comatose patients.

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